

Salt Intake Is Associated with Inflammation in Chronic Heart Failure

Alper Azak^{1,*}, Bulent Huddam¹, Namik Gonen², Seref Rahmi Yilmaz³, Gulay Kocak¹, Murat Duranay¹

¹Department of Nephrology, Ankara Education and Research Hospital, Ankara, Turkey

²Department of Internal Medicine, Ankara Education and Research Hospital, Ankara, Turkey

³Department of Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 22 Nov 2013
Revised: 13 Feb 2014
Accepted: 04 May 2014

Keywords:
Heart Failure
Inflammation
Sodium Dietary

ABSTRACT

Background: Chronic Heart Failure (CHF) is highly prevalent and is associated with high morbidity and mortality rates. It has been well established that excessive intake of sodium chloride (salt) induced hypertension in some populations. Although salt seems to induce cardiovascular diseases through elevation of blood pressure, it has also been indicated that salt can induce cardiovascular diseases independently from blood pressure elevation.

Objectives: The present study aimed to evaluate the association between salt consumption and inflammation in CHF patients.

Patients and Methods: This study was conducted on 86 patients between 18 and 65 years old who were diagnosed with New York Heart Association (NYHA) functional class I and II heart failure. Salt intake was calculated by using 24 hour urine sodium excretion. Besides, the association between inflammation and daily salt intake was evaluated regarding C - reactive protein (CPR), High sensitive CRP (HsCPR), Erythrocyte Sedimentation Rate (ESR), and ferritin and fibrinogen levels using Pearson correlation analysis.

Results: Our results showed a statistically significant difference between the low ($n = 41$) and high ($n = 45$) salt intake groups in terms of serum HsCPR levels (5.21 ± 2.62 vs. 6.36 ± 2.64) ($P < 0.048$). Additionally, a significant correlation was observed between the amount of salt consumption and HsCPR levels. In this study, daily salt consumption of the enrolled patients was 8.53 gram/day. The medications and even the blood pressures were similar in the two groups, but daily pill count, prevalence of hypertension, and coronary heart disease were higher in the high salt intake group; however, the differences were not statistically significant ($P = 0.065$). Also, no significant difference was observed between the groups concerning the inflammation markers, such as CRP, ESR, ferritin, and fibrinogen.

Conclusions: Neurohumoral and inflammatory factors are thought to contribute to high mortality and morbidity rates in CHF. Yet, inflammatory markers may early diagnose CHF and predict the prognosis. Excessive salt intake also worsens the inflammation as well as volume control.

► *Implication for health policy/practice/research/medical education:*

Our work is about the association of inflammation and salt intake in chronic heart failure patients. Salt restriction is recommended to these patients. This approach may also contribute to lower the degree of inflammation besides volume and blood pressure control. Even there has been no intervention in our study, our results show the association between salt intake and inflammation in patients with heart failure.

1. Background

Chronic Heart Failure (CHF) is highly prevalent in the

general population and is associated with high morbidity and mortality rates. The prevalence of CHF has been reported to be about 1 - 2% in the general population (1). It has long been recognized that CHF is associated with inflammatory cell activation (2-4).

*Corresponding author: Alper Azak, Balikesir State Hospital, Balikesir, Turkey, Tel: +90-5053841046,
E-mail: dralperazak@gmail.com

It has been well established that excessive intake of sodium chloride (salt) induced hypertension in some populations. Although salt seems to induce cardiovascular diseases through the elevation of blood pressure, it has also been known that salt can induce cardiovascular diseases independently from blood pressure elevation (5).

Nutritional factors in heart failure may be related to the pathophysiology of the disease, including inflammation. However, the association between salt consumption and inflammation has not been evaluated in the patients with CHF. Being a major contributing factor to high mortality rates in CHF, inflammation may be enhanced by high salt intake.

2. Objectives

Therefore, the present study aims to evaluate the relationship between salt intake and inflammation in the patients with CHF.

3. Patients and Methods

This study was conducted on 95 patients between 18 and 65 years old who were diagnosed with New York Heart Association (NYHA) functional class I and II heart failure (6). Nine patients were excluded due to loss of data. The exclusion criteria of the study were the presence of chronic inflammatory disease, infection, uric acid metabolism disorders, malignancy, anemia, diuretic use, and estimated glomerular filtration rate lower than 60 mL/min calculated using the MDRD Formula (7).

Echocardiography was performed before blood samples were collected for serum analysis. Salt intake was computed using 24 hour urinary sodium extraction. Serum levels of High sensitive C - reactive protein (HsCRP), C - reactive protein (CRP), fibrinogen, ferritin, Brain Natriuretic Peptide (BNP), aldosterone, and homocysteine were measured, as well.

3.1. Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 12.0 (SPSS inc., Chicago, IL, USA) was used for all the statistical analyses. The data are presented as mean \pm standard deviation for continuous variables, and as percentages for the categorical ones. The scale data between the groups

were analyzed using unpaired Student's T test. In addition, Pearson correlation coefficient was used to analyze the correlations. Besides, one-way ANOVA was used to make comparisons between sodium/creatinin groups.

4. Results

This study was conducted on 86 patients (29 males, 57 females). The patients' demographic characteristics, comorbidities, and medications have been listed in Table 1.

The patients were divided into three groups according to their 24 hour urine sodium/creatinine ratio (Group I < 100 mEq/g, n = 18, 20.9%; group II 100 - 200 mEq/g, n = 45, 52.3%; group III > 200 mEq/g, n = 23, 26.7%). The 24 hour urine sodium/creatinine ratios were 76.05 ± 12.83 , 143.07 ± 28.03 , and 252.93 ± 43.49 in groups I, II, and III, respectively. Besides, serum HsCRP levels were higher in group III compared to groups I and II and the difference was statistically significant (Table 2).

In order to evaluate the association between inflammation and daily salt intake, the patients were compared in terms of CRP, HsCRP, ESR, ferritin, and fibrinogen. The results indicated a significant difference among the study groups regarding urinary sodium/creatinine ratio and serum HsCRP levels (Figure 1).

Serum uric acid levels were measured as 5.54 ± 1.55 , 5.8 ± 1.77 , and 7.81 ± 0.86 in groups I, II, and III, respectively. Additionally, higher serum uric acid levels were detected in group III and the difference was statistically significant.

5. Discussion

The findings of the present study showed that 24 hour urinary sodium/creatinine ratio was highly correlated to serum HsCRP levels. Also, high sodium intake was associated with higher serum uric acid levels.

In the last decade, some improvements were made in understanding the pathophysiology and treatment of CHF. High mortality and morbidity rates in these patients imply that unexplained mechanisms may also play a role. It has been well known that compensatory mechanisms of CHF involve renal, neurohumoral, and renin-angiotensin-aldosterone system. Also, it has been hypothesized that persisted

Table 1. Demographic Characteristics and the Medications of the Patients

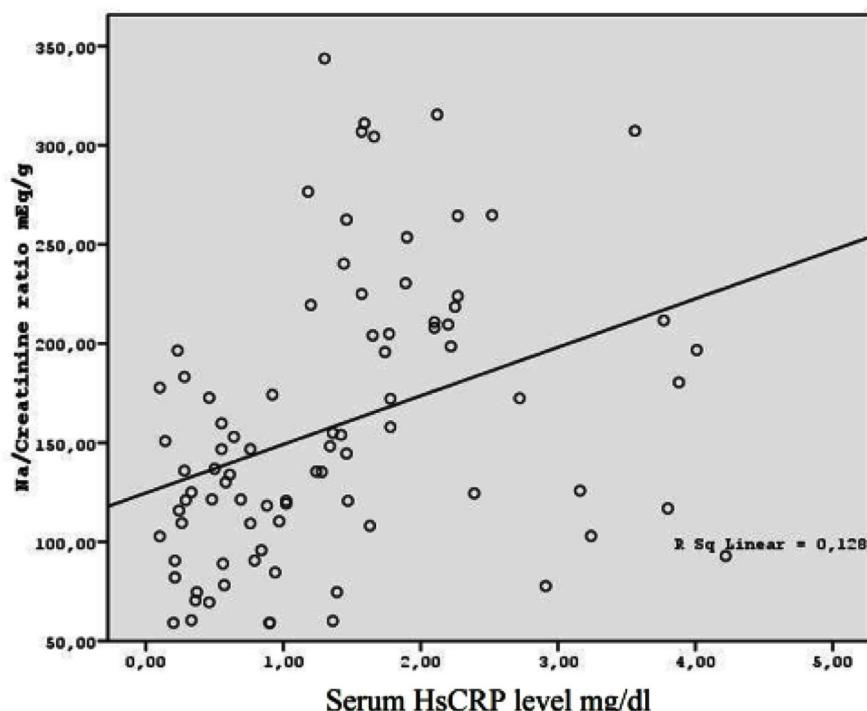
Sex	Female (n = 45)	Male (n = 41)	Total (n = 86)
Mean age (years)	64.51 ± 12.17	65.59 ± 8.02	64.87 ± 10.91
Diabetes mellitus	24 (53.3)	10 (24.3)	34
Hypertension	40 (88.9)	29 (70.7)	69
Coronary artery disease	14 (31.1)	7 (17)	21
Chronic kidney disease	4 (8.8)	4 (9.7)	8
Hyperlipidemia	13 (28.8)	3 (7.3)	16
ACEI	14 (31.1)	7 (17)	21
ARB	20 (44.4)	5 (12.1)	25
CCB	21 (46.6)	10 (24.3)	31
Beta Blocker	9 (20)	5 (12.1)	14
OAD	15 (33.3)	7 (17)	22
Insulin	7 (15.5)	2 (4.8)	9
ASA	9 (20)	6 (14.6)	15
Statin	9 (20)	3 (7.31)	12

Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker; OAD, Oral anti diabetic; ASA, Acetyl salicylic acid

Table 2. Study Groups' Characteristics Based on Their Urinary Sodium/Creatinine Ratio

	Group I (< 100 mEq/g, n=27)	Group II (100-200 mEq/g, n= 31)	Group III (>200 mEq/g, n=29)	P value
Sex (M/F)	14 / 13	16 / 14	15 / 14	0.086
Age	67.44 ± Kas.81	63.56 ± 10.9	65.43 ± 10.29	0.420
Systolic blood pressure	141.4 ± Kas.48	145.2 ± 15.2	144.13 ± 17.75	0.673
Diastolic blood pressure	83.11 ± 10.57	83.84 ± 6.4	85.65 ± 8.7	0.560
Antihypertensive agent count/day	2.3 ± 0.4	2.9 ± 0.5	3.01 ± 0.4	0.460
CRP (mg/dL)	0.97 ± 1.03	1.23 ± 1.06	1.97 ± 0.65 ^b	0.003
24 hour urine protein (mg/day)	226.9 ± 579.05	608 ± 218.29	554.2 ± 112.7	0.497
24 hour sodium/creatinin ratio	76.05 ± 12.8	143.1 ± 28.03	538.05 ± 197.8 ^{a,b}	< 0.01
proBNP (pg/mL)	109.4 ± 77.2	104.8 ± 70.1	106.97 ± 80.54	0.975
Aldosterone (pmol/L)	170.5 ± 64.36	165.4 ± 66.9	152.3 ± 50.42	0.607
Homocysteine (μmol/L)	14.8 ± 6.12	15.44 ± 6.75	15.16 ± 6.78	0.941
Fibrinogen	397.6 ± 56.03	408.9 ± 69.01	406.48 ± 70.91	0.830
Ferritin	73.24 ± 47.29	94.9 ± 63.6	68.63 ± 48.2	0.140
HsCRP	5.46 ± 3.36	5.6 ± 3.05	5.14 ± 3.26	0.780
Erythrocyte sedimentation rate/hour	22.28 ± 14.7	24.18 ± 17.5	20.3 ± 14.2	0.64
Hemoglobin	13.97 ± 1.29	13.85 ± 1.55	13.77 ± 1.32	0.900
Creatinine	1.09 ± 0.28	1.13 ± 0.35	0.86 ± 0.15	0.060
Sodium	140.6 ± 3.05	140.62 ± 2.8	140.96 ± 2.63	0.870
Potassium	4.11 ± 0.048	4.59 ± 0.51	4.55 ± 0.45	0.078
Uric Acid	5.54 ± 1.55	5.8 ± 1.77	7.81 ± 0.86 ^{b,c}	< 0.01
Albumin	4.2 ± 0.21	4.14 ± 0.33	4.07 ± 0.4	0.430
Microalbuminuric patient count	4	5	4	

^a, P < 0.05 Group I vs Group II; ^b, P < 0.05 Group I vs Group III; ^c, P < 0.05 Group II vs Group III

**Figure 1.** The Correlation between Serum HsCRP Levels and Na/Creatinin Ratio

immune system activation and inflammation may have crucial importance. Recent studies have focused on the negative effects of inflammation and circulating cytokines on cardiac inotropy and remodeling in course of CHF. In an animal model of dilated cardiomyopathy, it was shown that circulating inflammatory cytokines were increased (8-10). In SOLVD trial, it was found that CHF patients whose plasma TNF-alpha levels were below 6.5 pg/mL had

better survival rates (11). Also, TNF-alpha and IL-6 have been mentioned as independent predictors of mortality in CHF (3, 12).

Studies have also been conducted on the effectiveness of treatments. In PRAISE trial, amlodipine lowered IL-6 but not TNF-alpha and high dose enalapril lowered IL-6 levels. Additionally, β adrenergic stimulation increased IL-1 and TNF-alpha levels, while β blockade lowered these

inflammatory cytokines. Moreover, statin therapy lowered CRP levels (13).

In general, neurohumoral activation, aldosterone synthesis, and triggers of these two take place in pathophysiological fundamentals of CHF. Aldosterone that is significantly influenced by salt intake plays a role in pathophysiological mechanisms of both CHF and hypertension. Our study results showed no significant difference among the study groups regarding serum aldosterone levels. Also, no statistically significant difference was observed among the groups in terms of demographic characteristics and co-morbidities.

Dietary salt intake affects vascular endothelial independently from blood pressure. A study demonstrated that excessive salt intake in normotensive rats resulted in higher expression of endothelial TGF-beta (14).

In National Health and Nutrition Examination Survey (NHANES III), the patients with non-ischemic CHF were evaluated in terms of CRP and fibrinogen levels. According to the results, fibrinogen levels were higher in the CHF patients and also displayed a racial difference. In addition, the highest levels of fibrinogen were detected in non-Hispanic whites (15).

Microalbuminuria is a useful prognostic marker in evaluation of both diabetic and non-diabetic patients for renal and cardiovascular risk profiling (15-18). Microalbuminuria is thought to result from vascular endothelial damage and increased vascular permeability in kidneys and, consequently, may be an early predictor of atherosclerosis (19). A large number of studies have confirmed that microalbuminuria may predict cardiovascular mortality (20, 21). Moreover, the studies involving hypertensive and diabetic patients have demonstrated that microalbuminuria is associated with male sex, glycemic control, blood pressure, triglyceride levels, central obesity, smoking, diabetes vintage, and age (22, 23). Nevertheless, the current study indicated no relationships between microalbuminuria and sodium/creatinine ratio. Also, no significant relationship was found between microalbuminuria and salt intake in our study. This insignificant finding might be due to the fact that few patients were involved, even the patients' comorbidities were similar, and the vintage and stages of the diseases were not included. Since microalbuminuria is a strong predictive and prognostic factor for heart diseases, the relationship between this marker and salt intake is thought to be worth evaluating.

BNP is a protein which consists of 32 amino acids. It is primarily secreted as preproBNP after volume and pressure increases in the ventricles and is converted enzymatically into N-terminal proBNP (NT-proBNP) and BNP. Both NT-proBNP and BNP are used for diagnosis of congestive heart failure (24, 25). BNP can also be used as a prognostic marker in acute coronary syndrome (26). It has been shown that BNP may predict sudden cardiac death (25). Nonetheless, the current study results did not indicate any relationship between salt intake and BNP levels. It is possible that not only salt intake but also some other factors may have a role in secretion of BNP.

HsCRP is produced from the liver in case of systemic inflammation and is assumed as a new risk factor for atherosclerosis. Coronary atherosclerosis is manifested

by CHF. Alonso-Martinez et al. studied the relationship between NYHA CHF stages and Left Ventricle Ejection Fraction (LVEF) in hospitalized CHF patients. HsCRP levels were found to be reversely correlated to functional capacity and LVEF. Also, higher HsCRP levels were found to predict mortality and rehospitalization (14).

In National Health and Nutrition Examination Survey (NHANES III), fibrinogen and HsCRP levels were found to be higher in the patients with non-ischemic CHF compared to those without CHF (16). Howie et al. demonstrated that statin therapy improved left ventricle performance in ischemic and non-ischemic serious CHF patients. Moreover, HsCRP levels were found to be correlated to higher mortality and rehospitalization rates. In addition to the positive pleiotropic effects of statins, lower HsCRP levels may also be a contributing factor (27).

Our study results showed that salt intake was correlated to HsCRP levels. This implies that increased salt intake may play a role in the neurohumoral and the physiopathological pathways of CHF besides increasing the volume load. Thus, it may be hypothesized that salt restriction may improve the inflammatory process besides improvements in the volume load and hypertension.

Recent studies have supported the effectiveness of inflammatory markers and cytokines in CHF physiopathology by negative inotropic impact and remodeling.

The present study also revealed no relationship between salt intake and other inflammation markers, except for HsCRP. The positive correlation between salt intake and HsCRP makes us think that salt intake may contribute to inflammatory damage in CHF. Yet, the effect of salt restriction on the inflammation status needs to be further investigated.

5.1. Limitations

The main limitation of the present study was the absence of a control group. Another limitation of the study was the number of the patients involved in this study. Also, evaluation of salt intake and inflammation by using the stages of CHF was not performed; early and late stages of CHF may show a different association in terms of salt intake and inflammation.

Acknowledgements

There is no acknowledgment.

Authors' Contribution

Study concept and design: Rahmi Yilmaz; Acquisition of data: Alper Azak, Namik Gonen, Levent Ortabozkoyun; Analysis and interpretation of data: Alper Azak, Gulay Kocak; Drafting of the manuscript: Alper Azak, Bulet Huddam; Critical revision of the manuscript for important intellectual content: Alper Azak, Bulet Huddam; Statistical analysis: Alper Azak, Bulet Huddam; Administrative, technical, and material support: Alper Azak, Bulet Huddam, Rahmi Yilmaz; Study supervision: Murat Duranay

Financial disclosure

Authors declare that they have no conflict of interest.

Funding/Support

There is no funding/support.

References

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93(9):1137-46.
2. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation*. 2001;103(16):2055-9.
3. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med*. 1990;323(4):236-41.
4. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation*. 2000;102(25):3060-7.
5. Safar ME, Thuilliez C, Richard V, Benetos A. Pressure-independent contribution of sodium to large artery structure and function in hypertension. *Cardiovasc Res*. 2000;46(2):269-76.
6. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119(14):e391-479.
7. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007;53(4):766-72.
8. Aukrust P, Ueland T, Lien E, Bendtzen K, Muller F, Andreassen AK, et al. Cytokine network in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1999;83(3):376-82.
9. Bozkurt B, Kribbs SB, Clubb FJ, Jr., Michael LH, Didenko VV, Hornsby PJ, et al. Pathophysiologically relevant concentrations of tumor necrosis factor-alpha promote progressive left ventricular dysfunction and remodeling in rats. *Circulation*. 1998;97(14):1382-91.
10. Testa M, Yeh M, Lee P, Fanelli R, Loperfido F, Berman JW, et al. Circulating levels of cytokines and their endogenous modulators in patients with mild to severe congestive heart failure due to coronary artery disease or hypertension. *J Am Coll Cardiol*. 1996;28(4):964-71.
11. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol*. 1996;27(5):1201-6.
12. Cohn JN, Goldstein SO, Greenberg BH, Lorell BH, Bourge RC, Jaski BE, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. *N Engl J Med*. 1998;339(25):1810-6.
13. Mohler ER, 3rd, Sorensen LC, Ghali JK, Schocken DD, Willis PW, Bowers JA, et al. Role of cytokines in the mechanism of action of amlodipine: the PRAISE Heart Failure Trial. Prospective Randomized Amlodipine Survival Evaluation. *J Am Coll Cardiol*. 1997;30(1):35-41.
14. Kanbay M, Chen Y, Solak Y, Sanders PW. Mechanisms and consequences of salt sensitivity and dietary salt intake. *Curr Opin Nephrol Hypertens*. 2011;20(1):37-43.
15. Ying WZ, Sanders PW. Dietary salt increases endothelial nitric oxide synthase and TGF-beta1 in rat aortic endothelium. *Am J Physiol*. 1999;277(4 Pt 2):H1293-8.
16. Alonso-Martinez JL, Llorente-Diez B, Echegaray-Agara M, Olaz-Preciado F, Urbieta-Echezarreta M, Gonzalez-Arencibia C. C-reactive protein as predictor of improvement and readmission in heart failure. *Eur J Heart Fail*. 2002;4(3):331-6.
17. Ferketich AK, Binkley PF. Heart failure and inflammation: results from the third national health and nutrition examination survey (NHANES III). *Journal of Cardiac Failure*. 2004;10(4):S93.
18. Bakris G. Inclusion of albuminuria in hypertension and heart guidelines. *Kidney Int Suppl*. 2004(92):S124-5.
19. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560-72.
20. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2007;28(12):1462-536.
21. Yokoyama H, Sone H, Oishi M, Kawai K, Fukumoto Y, Kobayashi M. Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: the Japan Diabetes Clinical Data Management study (JDDM15). *Nephrol Dial Transplant*. 2009;24(4):1212-9.
22. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. *Arch Intern Med*. 1997;157(13):1413-8.
23. Patel KL, Mhetras SB, Varthakavi PK, Merchant PC, Nihalani KD. Microalbuminuria in insulin dependent diabetes mellitus. *J Assoc Physicians India*. 1999;47(6):589-95.
24. McCullough PA, Omland T, Maisel AS. B-type natriuretic peptides: a diagnostic breakthrough for clinicians. *Rev Cardiovasc Med*. 2003;4(2):72-80.
25. Wallen T, Landahl S, Hedner T, Nakao K, Saito Y. Brain natriuretic peptide predicts mortality in the elderly. *Heart*. 1997;77(3):264-7.
26. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med*. 2001;345(14):1014-21.
27. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. *J Am Coll Cardiol*. 2004;43(4):642-8.